quinazolinyl]methoxy]phenylmethyl] thiadiazolidine-2,4-dione is stated on page 1, lines 10-11 as being disclosed in PCT Publication WO 97/41097, the Lohray reference. As the Examiner is aware, this reference does not disclose 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenylmethyl] thiadiazolidine-2,4-dione; it discloses 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenylmethyl] thiazolidine-2,4-dione. One of ordinary skill in the art would recognize the existence of the error as well as its appropriate correction. Therefore, the amendment to the specification and claims would not constitute new matter

1. The Rejections Under 35 U.S.C. 103(a)

Claims 6, 7, 9, 11-13, 16 and 28-31 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Lohray et al. (WO 9741097) in view of Sohda et al. (U.S. Pat. No. 5972971). The Examiner asserts the following with respect to Lohray:

> The difference between above reference and Applicant's claiming [sic]invention is the usual pharmaceutically acceptable excipients such as talc, lactose being employed is anhydrose and the specific cellulose. Applicants' are claiming a well known composition modified with usual, pharmaceutically acceptable excipients routinely incorporated in a tablet form in a low water content. The Lohray reference prepared the composition employing process of drying the mixtures under the reduced pressure. Therefore, Lorhray's[sic] composition obviates Applicants' composition of low water content, without showing result of improved stability alleged by the Applicants
>
> For these reasons the claimed subject matter is deemed fail to patably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 5 U.S.C. 103.
>
> It is suggested that Applicants submit a declaration to clearly establish a surprising and unexpected result using Applicants teaching.

The Examiner states the following with respect to the secondary reference and combining the primary and secondary references.

> The difference between the primary reference and applicants' claimed invention is the presence of anti-oxidant set forth in claims 6, 14, and 15, and the proportions set forth in claims 8 an 9. However, to incorporate anti-oxidant to the primary reference would have been obvious to a person of ordinary skill in view of Sohda et al. who teach antidiabetic agent containing anti-oxidant and the other excipient. One in ordinary skill in the art would have been motivated to combine anti-oxidants to above composition since Lohray et al. teach other media normally employed can be incorporated and anti-oxidant is normally incorporated by Sohda et al. in formulating anti-diabetic agent.
>
> The proportions of active agents to be used, and adjusting water content of excipient are all deemed obvious since they are all within the knowledge of the skilled pharmacologist.
>
> For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.
>
> None of the claims are allowed.
>
> It is suggested, to advance the prosecution of the subject application, that a side by side comparison of stability be performed and results submitted per Rule 1.132 for review by the Patent Office.

In response, Applicants herewith submit a Declaration Under 37 C.F.R. §1.132 by one of the inventors, Thyge Borup Hjorth, showing that the low moisture content formulation does indeed have improved stability. Specifically, side by side comparisons were conducted with two formulations, where the only difference was the cellulose used. Specifically, formulations A and C used Avicel PH 102, a microcrystalline cellulose having a higher moisture content; formulations B and D used Avicel PH112, microcrystalline cellulose having a low moisture content. The data shows that at 40°C/75% RH, the formulations containing microcrystalline cellulose with low moisture content (Avicel PH 112, formulation B and D) are more stable i.e. lower content of degradation products than the formulations containing microcrystalline cellulose with higher moisture content (Avicel PH 102, formulation A and C). These results are certainly nonobvious and unexpected.

Applicants assert that the Sohda reference would not add anything further to the disclosure of Lohray. There is certainly no suggestion or disclosure in the Sohda et al. reference regarding the use of low moisture formulations. Furthermore, Applicants assert that one of ordinary skill in the art would not be motivated to combine Lohray et al. with Sohda et al. This is because Sohda et al. is directed to a completely different class of compounds, 2,4-oxazolidinedione compounds. Therefore, in the Applicants' view, any disclosures with respect to Sohda et al. would be considered by one of ordinary skill in the art to have limited relevance to the active compound in the formulations of the present invention, 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenylmethyl] thiazolidine-2,4-dione.

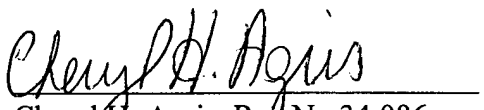
In view of the Declaration Under 37 C.F.R. §1.132 submitted and the above arguments, Applicants assert that the rejections under 35 U.S.C. §103(a) have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone at (914) 712-0093 if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: 8/23/02



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SUBSTITUTE SPECIFICATION-CLEAN VERSION

New pharmaceutical composition and the process for its preparation

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. 119 of Danish application PA 1998 01580 filed December 1, 1998 and of U.S. Provisional application 60/112,248 filed December 14, 1998, the contents of which are fully incorporated herein by reference.

The subject-matter of the present invention is a new pharmaceutical composition containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione as active ingredient and the process for its preparation.

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof has been found useful in the treatment of type 2 diabetes acting as a insulin sensitizer as disclosed in PCT Publication WO 97/41097.

The active ingredient is present as the base or as a pharmaceutically acceptable salt, preferably as the potassium salt.

Various solutions have been proposed for the preparation of medications based on 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione.

The aim of the present invention is to provide a new composition intended for the preparation of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione with improved stability, in particular solid dosage forms thereof.

It has been found in fact that 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quina-zolinyl]meth-oxy]-phenyl-methyl]thiazolidine-2,4-dione and its pharmaceutically acceptable salts may decompose in the presence of and in contact with water. Further it has been observed that decomposing may occur in the presence of oxygen.

Thus, from a first aspect, the subject-matter of the present invention is a pharmaceutical composition intended for the preparation of dosage forms and in particular solid dosage forms containing an efficacious quantity of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or of one of its pharmaceutically acceptable salts as active ingredient.

The present invention is based on the surprising discovery of the fact that the stability of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts, can be considerably improved in preparations containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or of its pharmaceutically acceptable salts and antioxidant agent if the product is composed of excipients which do not contain water.

Pharmaceutically acceptable salts forming part of this invention include salts such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, aluminium salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulplionates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, together with a conventional adjuvant, antioxidant carrier, or diluent, and if desired a pharmaceutically acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or oral powders to be diluted immediately before use filled with the same, all for oral use, in the form of suppositories for rectal administration; or as pessaries for vaginal use; or in the form of sterile injectable powders for parenteral, transdermal, nasal, pulmonary and ocular use.

Within the framework of the present description and of the claims, by powders is meant any mixture of components, granulated or not, intended to be placed in solution and/or in suspension in water, or again to be ingested directly or by any other appropriate means as for example in a mixture with a food product.

In accordance with a particular characteristic of the invention, the manufacture of tablets are carried out as a direct compression.

In accordance with another particular characteristic, this composition also contains pharmaceutically acceptable excipients.

In accordance with a particular characteristic of the invention, the antioxidant agent cited above is selected from among α-tocopherol, γ-tocopherol, δ-tocopherol, extracts of natural origin rich in tocopherol, L-ascorbic acid and its sodium or calcium salts, ascorbyl palmitate, propyl gallate (PG), octyl gallate, dodecyl gallate, butylated hydroxy anisole (BHA) and butylated hydroxy toluene (BHT).

In accordance with a currently preferred embodiment, the antioxidant agent will be α-tocopherol.

In accordance with another particular characteristic of the invention, the diluent is lactose and/or cellulose microcrystalline, magnesium stearate, talc.

However, any other pharmaceutically acceptable diluents could be used if the diluents has a low water content.

The quantities of diluents can be easily determined by a person skilled in the art and depend of course on the final pharmaceutical form required.

Generally speaking, a composition which complies with the present invention and which are intended for the preparation of tablets, may contain, expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts:

between 100 and 400,000 parts by weight of anhydrous lactose;
between 1 and 100 parts by weight of an antioxidant;
between 50 and 500 parts by weight of pregelatinized starch;
between 1000 and 10,000 parts by weight of microcrystalline cellulose;
between 10 and 500 parts by weight of crospovidone;
between 10 and 500 parts by weight of silicon dioxide;
between 10 and 500 parts by weight of hydrogenated vegetable oil;
between 10 and 500 parts by weight of magnesium stearate;
between 10 and 500 parts by weight of hydroxypropyl methylcellulose;
between 10 and 500 parts by weight of hydroxypropyl cellulose;
between 1000 and 10,000 parts by weight of Mannitol;
between 10 and 500 parts by weight of stearic acid;
between 10 and 500 parts by weight of Titanium Dioxide;

According to a preferred embodiment of the invention the water content of the excipients is very low. More specifically the water content in the diluents is very low in order to minimize the water content of the pharmaceutical composition. Lactose is used in its anhydrous form.

Furthermore, all excipients may be applied in a dry form.

In accordance with a second aspect, the subject-matter of the present invention is a pharmaceutical preparation, in the form of tablet or powder, characterised in that it contains a composition as defined previously associated if required with at least one customary additive selected from among the sweeteners, flavouring agents, colours and lubricants.

The choice of these additives and their quantity can easily be determined by a person skilled in the art.

Another manufacturing process for pharmaceutical compositions according to the invention is mixing of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, one or more antioxidants and other pharmaceutical excipients followed by melt granulation in a high shear mixer. Hydrogenated, vegetable oil, waxes or other low temperature melting binders can be used. The granules can be filled into capsules, compressed into tablets or used in other pharmaceutical dosage forms.

More preferably the manufacturing process applied is direct compression of tablets, wherein 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, one or more antioxidants and other excipients suitable for direct compression are mixed followed by tabletting.

Yet, another preferred embodiment of the manufacturing process is wet granulation, where granules are obtained by wet massing of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, together with one or more antioxidants and other excipients.
It is assumed that the contact time with water have to be very short.

The most preferred process comprises the direct compression whereby 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione is kept at conditions of low water vapour pressure.

A sweetener may be a natural sugar such as sorbitol or a synthetic product such as saccharine or aspartame.

When the antioxidant selected is ascorbylpalmitate, propylgallate, which is a powder, it can be advantageous to mix it in an appropriate excipient such as α-tocopherol succinate, lactose or cellulose microcrystalline.

The present invention will further be illustrated with the following non-exhaustive examples.

In Example 1 through 4 the tablets were prepared according to the following procedure:

The active ingredient is mixed with cellulose microcrystalline in a drum mixer for 10 minutes.
Lactose is added and the mixing continued for further two minutes.
The lubricants are added and the mixing continued for further two minutes.

EXAMPLE 1

25 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt Tablets 807227

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt, 003/97	9%
Cellulose Microcrystallline	20%
Lactose	66%
Magnesium Stearate	0.5%
Talc	4.5%

EXAMPLE 2

50 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt tablets 807237

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt, 003/97	18%
Cellulose Microcrystalline	20%
Mannitol	57%
Magnesium Stearate	0.5%
Talc	4.5%

EXAMPLE 3

50 mg 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt Tablets 731725

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt	18%
Lactose	81.5%
Magnesium stearate	0.5%

EXAMPLE 4

0.25 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt Tablets 728625

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt	0.09%
Mannitol	98%
Magnesium stearate	2%

EXAMPLE 5

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt	0.09%
Hydrogenated vegetable oil	6.25%
Talc	5%
α-tocopherol	50% of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt
Lactose DCL21/Mannitol	Up to 200 g

The granulate is manufactured in a Baker Perkins 1 L high-shear mixer - using a water bath of 70°C. The mixing is carried out at 3000 RPM, chopper 6000 RPM and the granulation is performed at approx. 70°C. The hot granulate is sieved through sieve 1.25 μm, and the cold

granulate through sieve 1000 μm. The glidant is added with a card for 2 min. The tablets are manufactured using a Diaf tablet machine with 9 mm punch.

In order to protect against light and improve the appearance of the tablets, the tablets are film-coated.

The tablets were coated with the following film-coating composition where an amount of coating material of 5 mg/cm2 were chosen as being satisfactory with respect to stability of the tablets:

Methylhydroxypropylcellulose, Ph. Eur.....		~ 4.34 mg/tablet
Titanium Dioxide, Ph. Eur.....	~ 1.73	-
Purified Water, Ph. Eur.....		q.s. -

Talc, Ph. Eur. (Added as polishing agent at the end of the film-coating process (0.5 % w/w of tablet core). Absorbed amount is not quantified.

EXAMPLE 6

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, potassium salt	0.09%
Povidone	7.5%
Hydroxypropylmethyl cellulose	1.5%
Croscarmelose sodium	1.56%
Talc	1.1%
Magnesium stearate	0.5%
Lactose 300 mesh	up to 200 g

The granulate is manufactured by Baker Perkins 1 L intensive mixer. Dry mixing were carried out at 500 RPM, chopper 1500 RPM and granulation 1000 RPM and 2000 RPM. The wet granulate is sieved through sieve 1.25 μm and the dry granulate through sieve 1000 μm. The glidant is admixed with a card for 2 min. The tablets are manufactured by Diaf tablet machine with 9 mm punch.

EXAMPLE 7

Composition: Oral Powder, 1 mg/ml, 100 ml

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione potassium salt 0.1096 g
Mannitol 2.5 g
Hydroxypropyl-β-cyclodextrin 10 g

To be diluted with 92 mL water before use.

EXAMPLE 8

Composition: Oral Powder, 10 mg/ml, 100 ml

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione potassium salt 1.096 g
Mannitol 2.5 g
Hydroxypropyl-β-cyclodextrin 10 g
Sodium Carbonate, anhydrous, Na2CO3 15 mg

To be diluted with 92 mL water before use.

WHAT IS CLAIMED IS:

6. A pharmaceutical composition comprising
5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof,
and pharmaceutically acceptable excipients with low water content comprising anhydrous lactose, microcrystalline cellulose, magnesium stearate, and talc..

7. The pharmaceutical composition according to claim 6 in the form of a tablet, a powder or a capsule.

9. The pharmaceutical composition according to claim 6 wherein the pharmaceutically acceptable excipients are between 100 and 400,000 parts by weight of anhydrous lactose, between 1000 and 10,000 parts by weight of microcrystalline cellulose, and
between 10 and 500 parts by weight of magnesium stearate,
expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts.

11. The pharmaceutical composition according to claim 6 wherein the pharmaceutically acceptable excipients have a low water content.

12. The pharmaceutical composition according to claim 6 wherein the pharmaceutically acceptable excipients have a very low water content.

13. The pharmaceutical composition according to claim 6 wherein the pharmaceutically acceptable excipients are in a dry form.

16. The pharmaceutical composition according to claim 6 , further comprising at least one sweetener, flavouring agent, colour or lubricant.

28. The pharmaceutical composition according to claim 6 in tablet form, wherein the tablet is formed by direct compression.

29. The pharmaceutical composition according to claim 6 consisting of

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenylmethyl] thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof	9%
Microcrystalline cellulose	20%
Anhydrous lactose	66%
Magnesium Stearate	0.5%
Talc	4.5%

30. The pharmaceutical composition according to claim 29 in the form of a tablet, a powder or a capsule.

31. The pharmaceutical composition according to claim 30 in tablet form, wherein the tablet is formed by direct compression.

ABSTRACT

The present invention provides a new stable pharmaceutical composition containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione as active ingredient.